tissue microarray, the lower expression of PITX1 was found to be significantly linked to higher tumor stages. Additionally, increased PITX1 expression was found in a NSCLC cell line H2228 and a SCLC cell line H526 after they were exposed to the differentiation modifying agent BrdU indicating the potential role of PITX1 in lung cancer differentiation and carcinogenesis (Chen et al. 2007c).

LAGY/HOP, a novel tumor suppressor in lung cancer.

Previously, we first isolated the full-length sequence of LAGY/HOP and observed that this gene was downregulated in a panel of lung cancer cell lines as well as in a majority of primary lung tumors (Chen et al. 2003). Recently, we constructed an expression vector containing the full-length cDNA of LAGY/HOP and transfected it into the lung cancer cell line H2170. Stable transfection led to an increased expression of LAGY/HOP. LAGY/HOP positive transfectants remarkably reduced the growth rate and the ability of anchorage-independent growth in soft agar, and moreover suppressed the tumor formation in nude mice. Transient transfection of Nkx2.1 into H2170 resulted in the overexpression of LAGY/HOP, and correspondingly, siRNA silencing of Nkx2.1 reduced the expression of LAGY/HOP in lung cancer cells. Furthermore, increased expression of LAGY/HOP was observed in the BrdU modified differentiation cell model. Our data suggest that LAGY/HOP is a potential tumor suppressor possibly involved in lung cancer differentiation, and functions downstream of Nkx2.1 (Chen et al. 2007d).

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E02-02 Molecular Oncology: Implications for Clinical Practice, Sept 3, 16:00 – 17:30

Prognostic and predictive markers in lung cancer-emphasis on receptor tyrosine kinases egfr and met

Salgia, Ravi

University of Chicago, Chicago, IL, USA

Genetic and proteomic profiling of lung cancer has given way to a number of molecularly targeted therapeutics. As new molecules are identified to be important in lung cancer, we will need to determine their role as prognosticators and ultimately as predictive markers. A prognostic marker helps determine the progression of lung cancer and ultimate outcome; whereas, a predictive marker represents how a patient may respond to a particular type of treatment. Studies of receptor tyrosine kinases (RTKs), such as epidermal growth factor receptor (EGFR) and Met, have also lead to therapeutic target inhibition in solid tumors. In particular, overexpression of EGFR is a poor prognosticator in a number of solid tumors, especially lung cancer. Using small molecule inhibitors (such as erlotinib) and antibody (such cetuximab) against EGFR, a number of predictive markers have been utilized. The predictive markers can include expression of EGFR, phosphorylated EGFR, and downstream targets such as Akt via immunohistochemistry (IHC). Predictive markers for EGFR therapies also include gene amplification (with FISH) and mutational analysis. In spite of a large number of studies on EGFR and EGFR inhibitors, there is no clear consensus on the use of predictive markers. Some important facts that are emerging: 1. Mutational status of EGFR is predictive of response; 2. FISH is predictive of survival; 3. K-ras mutation is a negative predictor; 4. Rash is prognostic but not necessarily predictive. Met is another RTK that is overexpressed in lung cancer, sometimes amplified, as well potentially mutated. The mutations of Met rarely occur in the tyrosine kinase domain in lung cancer; however, a large number of mutations are in the semaphorin domain as well in the juxtamembrane (JM) domain. These mutations lead to gain of functions, and there appears to be a difference in mutations in various histologies as well in different ethnic backgrounds. We have identified that Met and its ligand, hepatocyte growth factor (HGF), are important prognosticators in lung cancer. There are several inhibitors agains Met/HGF that are already in clinical trials. It is to be determined with the various Met inhibitors if there are also predictive markers, and this will be discussed. Certainly, there are a large number of markers that are prognostic/predictive in lung cancer (such as the recently identified ERCC1 and RRM1; and a plethora of other gene/protein markers); however, rigorous prospective validation of biological and clinical markers of sensitivity needs to be performed.

E02-04 Molecular Oncology: Implications for Cl. Practice, Mon, Sept 3, 16:00 – 17:30

Molecular signature of lung cancer

Yang, Pan-chyr

National Taiwan University College of Medicine, Taipei, Taiwan

Lung cancer is the most serious cause of cancer mortality worldwide. The current clinical staging system can not accurately predict risk of patients. To develop an outcome prediction method for personalized therapy of lung cancer is the most important goal of cancer genomics.. To identify gene signature that can predict survival and metastasis in lung cancer patients, we examined the gene expressions in surgical specimens of 125 NSCLC patients using microarray and real-time RT-PCR and correlated with survival of the patients. We used the risk score and decision-tree methods to develop a gene-expression predictive model to predict the clinical outcome of NSCLC. We have identified sixteen genes that correlated with patient survival. We then selected 5 genes (DUSP6, MMD, STAT1, ERBB3 and LCK) and developed a risk predictive model based on RT-PCR and decision-tree approach. The 5-gene signature is an independent predictor of cancer recurrence and overall survival of NSCLC patients. We validated the model in an independent cohort of 60 NSCLC patients and also in an independent set of 86 western patients from published microarray data. This study can identify the patients with high risk gene signature in early stage. It may be a useful tool for risk prediction and designation of adjuvant treatment for high risk patients after validation in a prospective clinical trial. To move a step forward, we identified a unique microRNA signature that can predict the survival and relapse of 112 NSCLC

patients. We re-confirmed these findings in an independent cohort of 56 NSCLC patients. The microRNA signature can distinguish high or low-risk patients with significantly different survival within stage I, II, III, adenocarcinoma or squamous cell carcinoma subgroups of NSCLC patients. Our study supports the concept that cancer genomics has great potential for clinical application of personalized therapy.

We also used microarray and lung cancer invasion/metastasis cell line model to identify novel biomarkers and treatment targets of lung cancer. We have identified two invasion/metastasis suppressors: CRMP-1 and HLJ1. The microarray pathway analysis also helps to uncover their action mechanisms. The HLJ1-expression inhibited lung cancer cell proliferation, tumorigenesis, angiogenesis, cell motility, invasion and slowed cell cycle progression through a novel HLJ1/STAT1/ P21 WAF1 pathway that is P53 and interferon independent. The HLJ1 is co-regulated by YY1 at enhancer and AP1 at enhancer. HLJ1-expression is associated with reduced cancer recurrence and prolonged survival of NSCLC patients. These gene signatures and novel biomarkers can be used to predict clinical outcome and are potential treatment targets for lung cancer patients.

Session E03: What's new in Systemic Therapy?

E03-01 **What's new in Systemic Therapy? Mon, Sept 3, 16:00 – 17:30**

New cytotoxics

Gatzemeier, Ulrich

Center for Pneumology and Thoracic Surgery, Hospital Grosshansdorf, Grosshansdorf, Germany

Platin doublets are the standard of care in first line chemotherapy of advanced Non small cell lung cancer. The 1-year survival that can be achieved by chemotherapy is around 40 %.

During the past few years the major goal to improve the survival data was to include targeted therapies and drugs in the treatment strategy of NSCLC.

Stepwise success has been observed with several drugs like EGFR inhibitors. Nevertheless, new cytotoxics are under development as well to improve even efficacy and optimize toxicity with increased QOL during the treatment course.

Novel taxanes:

Docetaxel/Paclitaxel are standards in 1st line combination and as single agents in 2nd line treatment for NSCLC. There are limitations for both drugs in efficacy, tolerability and feasibility. Drug-conjugates might increase accumulation in tumors through enhanced permeation. Additionally there is no need for toxic solubilizing agents.

During the last few years we have some new compounds

Albumin bound Paclitaxel (Abraxane)

Makromolecule drug conjugate (Xyotax)

Oral Taxanes (BMS 275183,BAY 598862)

Xyotax was examined within 4 large phase III trials in 1st and 2nd line in NSCLC.

Study design: Stellar 2 (2nd line): Xyotax vs Docetaxel

Stellar 3 (1st line): Xyotax/Carbo vs Paclitaxel/Carbo

Stellar 4 (PS2): Xyotax vs Gemcitabine or Vinorelbine

Pioneer : Xyotax vs Paclitaxel

The results so far available showed similar survival,TTP, DCR. In women there was a trend towards increased survival. Regarding toxicity there was less myalgia and arthralgia,less alopecia,more nausea and vomiting,more grade Ê thrombocytopenia and delayed time to neuropathy.

Abraxane was found to have clinical advantages in comparison to Paclitaxel in metastatic breast cancer. The phase I/II program in NSCLC is finished. The drug has activity in NSCLC as sinle agent and in combination. A phase III program is under development.

The oral Taxanes are under investigation still in the phase I/II trials.

Epothylones:

The rationally designed, fully synthetic epothilone ZK-EPO has demonstrated activity against non small cell lung cancer cell lines. The results of the first completed Phase I study (one 30-min infusion q3w) demonstrated good tolerability, with peripheral neuropathy as the most common toxicity. Signs of activity, including a promising number of objective responses, were reported. A randomised Phase II trial was performed to determine the efficacy and safety of ZK-EPO as second line therapy (one 3-hour infusion q3w) in patients with stage IIIB and IV non small cell lung cancer.

A total of 44 patients have entered the study. A total of 113 infusions were administered to patients. 4 of the first 38 evaluable patients did show response. The most common drug-related toxicity was peripheral sensory neuropathy (< grade 3 in 45% of patients, grade 3 in 14%). Seven patients discontinued treatment due to neuropathy. Other drug-related toxicities (≥ 5%) were myalgia(23%), alopecia (18%), nausea (16%), fatigue (16%), vomiting (14%), constipation (9%), arthralgia (5%), fever (5%), dizziness (5%), diarrhea (5%), anorexia (5%).

Although the envisaged activity mark was not reached, this preliminary data indicate that ZK-EPO, administered as a 3-hour infusion at a dose of 16 mg/m^2, has promising activity as second line treatment of non small cell lung cancer. Peripheral neuropathy currently appears to be the only noteworthy toxicity of ZK EPO.

Pemetrexed:

Pemetrexed is approved in 2nd line treatment in NSCLC. There is reasonable activity and good safety profile.

Nevertheless there are a lot of open questions

activity in 1st line combinations

role of pemetrexed combinations in the adjuvant setting

combined modality treatment + radiotherapy in locally advanced inoperable NSCLC

A lot of randomized trials are underway to answer these questions. Some results might be available at the conference.

Customized therapy:

Another aspect to improve chemotherapeutic results during the last few years was to develop Ïcustomized therapiesÓ based on pharmacogenomic data to select patients with NSCLC having the chance to optimize standard chemotherapy.

ERCC1 and RRM1 (DNA repair-enzymes) are such markers which have been tested within clinical trials to select patients with platinum- or gemcitabine resistance.

High ERCC1 level are correlated with poorer survival after platinum-based chemotherapy.

Low RRM1 level seemed to be a sign for better gemcitabine-efficacy.

These data must be confirmed within large phase III trials in the future.